

Mixed chimerism and acceptance of kidney transplants after immunosuppressive drug withdrawal.

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Funding Grants: Induction of Tolerance to Combined Kidney and Hematopoietic Progenitor Cell Transplants from HLA Haplotype Matched Living Donors

Public Summary:

The rejection of transplanted organs is typically prevented by keeping patients on drugs that suppress the immune system's normal responses after transplant. However, immune suppression (IS) has significant long-term health consequences for the patient. Pre-clinical studies have shown that giving blood forming cells from the donor into the recipient may establish tolerance to the donor's cells by making the recipient's immune system chimeric in which immune cells of the recipient and the donor are both present. This state of mixed chimerism can result in tolerance to the transplanted organ eliminating the need for the patient to stay on life-long immune suppression. To determine whether persistent mixed chimerism and tolerance can be established in patients undergoing living donor kidney transplantation, we infused kidney recipients with T cells and hematopoietic progenitor cells from their donors. After undergoing kidney transplant, each patient was treated first with lymphoid irradiation followed by infusion of the donor's cells. In 24 of 29 fully human leukocyte antigen (HLA)-matched (6 out of 6 HLA types matched) patients, who developed persistent mixed chimerism for at least 6 months, complete IS drug withdrawal was achieved without subsequent evidence of graft rejection for at least 2 years, and for an observation period of up to 13 years. We then proceeded to treat patients who were not fully HLA-matched with their donors. These patients were HLA haplotype matched (mismatched for 1,2, or 3 out of 6 HLA types). In these patients, 10 of 22 developed persistent mixed chimerism for at least 12 months. These patients successfully underwent IS drug dose reduction and discontinuation of their IS drugs so only a single drug, tacrolimus, was still being taken. Withdrawal of tacrolimus during the second year resulted in loss of detectable chimerism and subsequent rejection episodes unless tacrolimus therapy was reinstituted. Further assessment showed the patients underwent immune reconstitution of naive B cells and B cell precursors more rapidly than the reconstitution of naive T cells and T cell precursors. Robust chimerism was observed only among naive T and B cells but not among memory T cells. No evidence of rejection was observed in graft biopsies obtained from mixed chimeric patients withdrawn from IS drugs. In addition, none of the patients developed graft-versus-host disease caused by the donor T cells. In conclusion, persistent mixed chimerism established in fully HLA- or haplotype-matched patients allowed for complete or partial IS drug withdrawal without rejection.

Scientific Abstract:

Preclinical studies have shown that persistent mixed chimerism is linked to acceptance of organ allografts without immunosuppressive (IS) drugs. Mixed chimerism refers to continued mixing of donor and recipient hematopoietic cells in recipient tissues after transplantation of donor cells. To determine whether persistent mixed chimerism and tolerance can be established in patients undergoing living donor kidney transplantation, we infused allograft recipients with donor T cells and hematopoietic progenitors after posttransplant lymphoid irradiation. In 24 of 29 fully human leukocyte antigen (HLA)-matched patients who had persistent mixed chimerism for at least 6 months, complete IS drug withdrawal was achieved without subsequent evidence of rejection for at least 2 years. In 10 of 22 HLA haplotype-matched patients with persistent mixed chimerism for at least 12 months, reduction of IS drugs to tacrolimus monotherapy was achieved. Withdrawal of tacrolimus during the second year resulted in loss of detectable chimerism and subsequent rejection episodes, unless tacrolimus therapy was reinstituted. Posttransplant immune reconstitution of naive B cells and B cell precursors was more rapid than the reconstitution of naive T cells and thymic T cell precursors. Robust chimerism was observed only among naive T and B cells but not among memory T cells. No evidence of rejection was observed in all surveillance graft biopsies obtained from mixed chimeric patients withdrawn from IS drugs, and none developed graft-versus-host disease. In conclusion, persistent mixed chimerism established in fully HLA- or haplotype-matched patients allowed for complete or partial IS drug withdrawal

without rejection.

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